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2/16/23

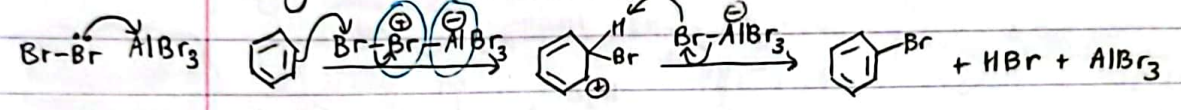
*draw lone pairs, be explicit w/ arrows!

Orgo Exam #1 Notesheet

EAS steps:

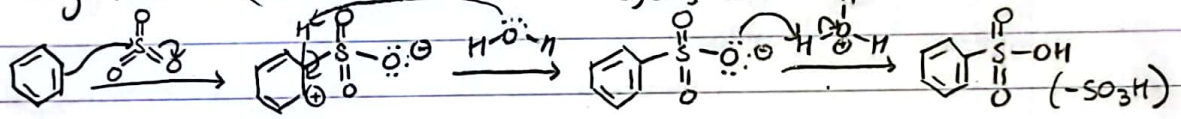
1) nucleophilic attack on $E^{\oplus}$ (slow) (breaking aromaticity) $C^{\oplus}$
2) deprotonation (E1) to restore aromaticity

Halogenation of Benzene:



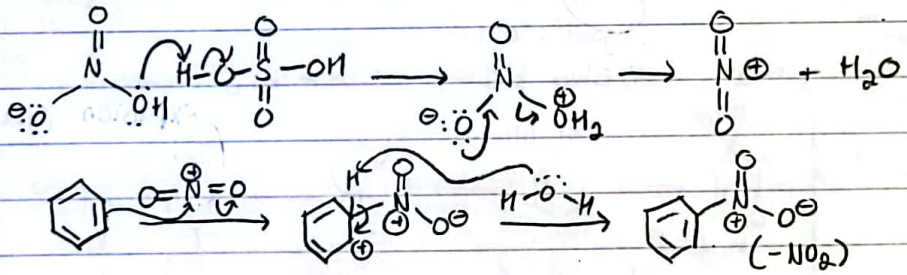
Sulfonation of Benzene:

"fuming H_2SO_4" → ($SO_3 + H_2SO_4$)

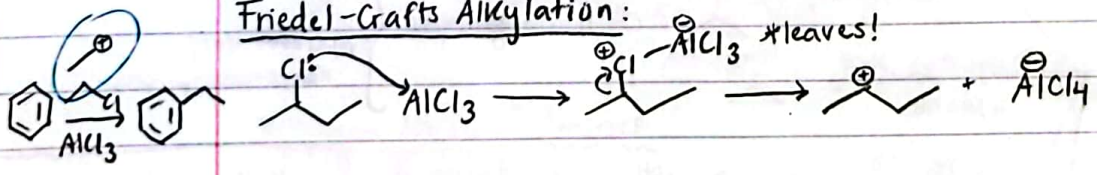


*sulfonation is reversible! (dilute H_2SO_4, Δ)
1) water removes H
2) double bond interacts w/ $H_3O^{\oplus}$
3) SO_3 leaves

Nitration of Benzene: ($HNO_3 + H_2SO_4$)

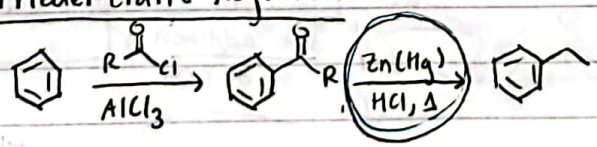


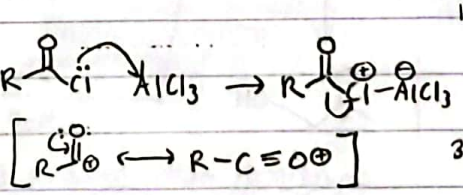
Friedel-Crafts Alkylation:



limitations:
1) $C^{\oplus}$ rearrangements will occur!
2) can't stop at just one alkylation!

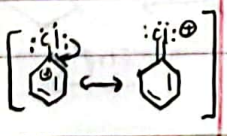
Friedel-Crafts Acylation:





notes:
1) no $C^{\oplus}$ rearrangements!
2) can convert acyl → alkyl
3) always stops after one acyl group
4) doesn't work on deactivated benzene

(activating) → o, p
- EDG - places ⊖ around ring
- EWG - places ⊕ around ring (deactivating) → m (keep ⊕ away from EWG AFTER $E^{\oplus}$) — think about stability of intermediates!



*halogens are EWGs via induction → weakly deactivating
but EDG via resonance → o, p

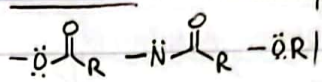
*label groups w/ strength & directing effects!

*strongest activator takes priority → flip! determines regioselectivity even if there's a strong deactivator

Activating Groups

Strong:

Moderate:

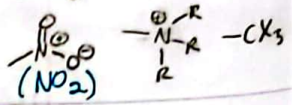


Weak:

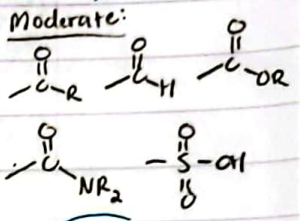
-R (alkyl)

Deactivating Groups

Strong:



Moderate:



$-C\equiv N$

Weak:

-X (halogen)
o, p

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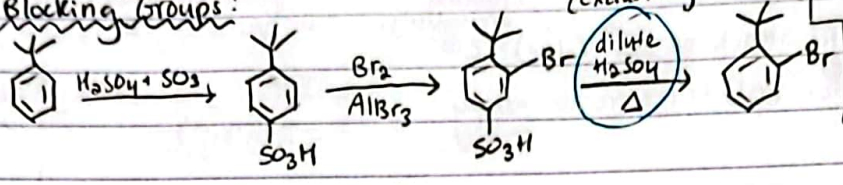
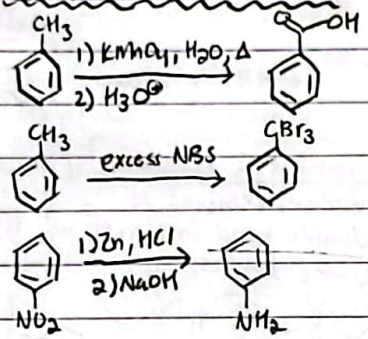
OIL RIG
formal charge : vust
oxidation states:
1) bonds to atoms w/ same eN = ignored
2) +I → more eN
3) -I → less eN
4) Add f.c. of atom (if it has one)

"Blocking" Groups:

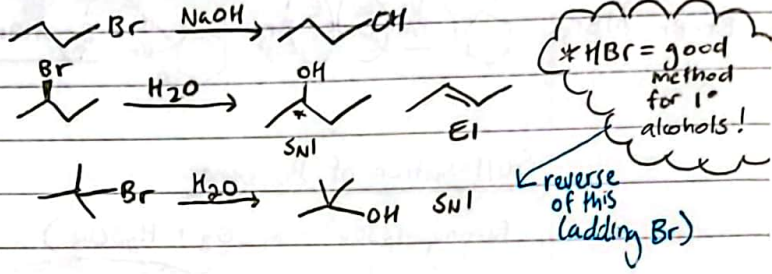


Useful Transformations:

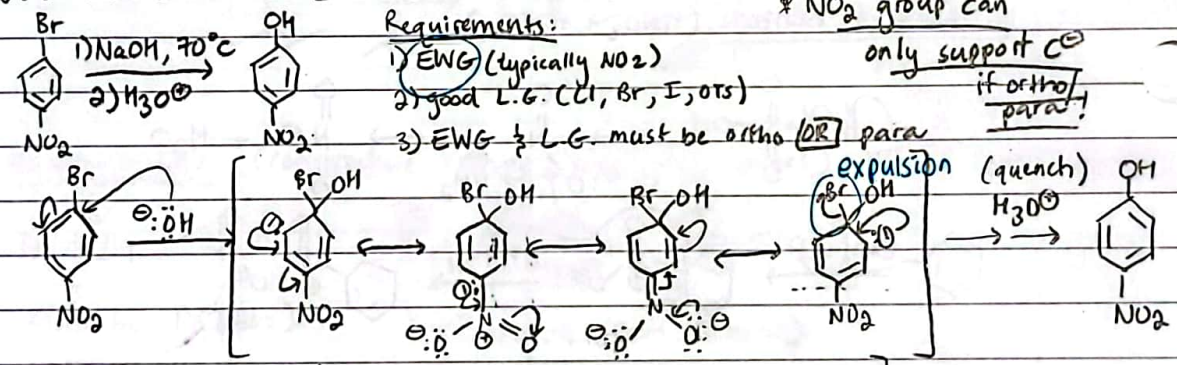
*can't do F-C on a deactivated ring! (more than weakly deactivated)



Preparation of Alcohols (something attached w/ Br)

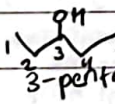


Nucleophilic Aromatic Substitution (S_NAr):

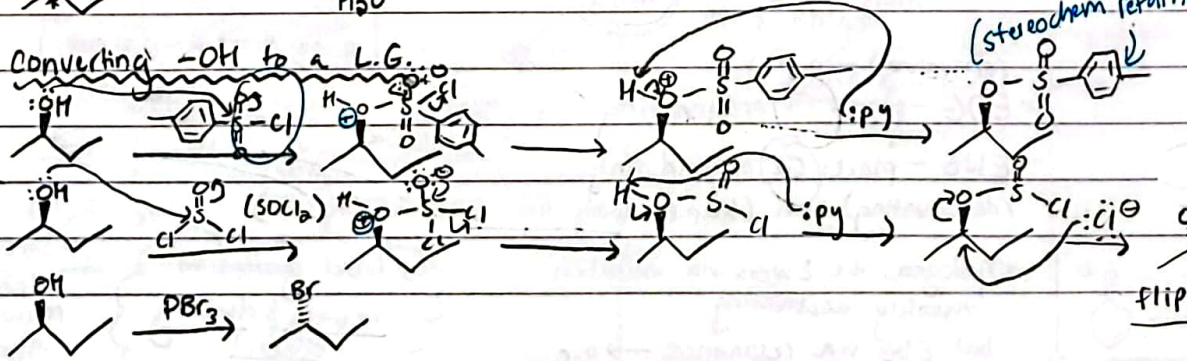


Naming Alcohols

*label groups, remember to alphabetize!
*assign locant # to -OH group



Converting -OH to a L.G.



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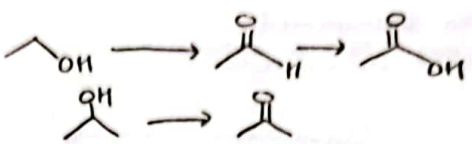
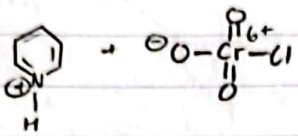


*count your carbons w/ intramolecular rxns!

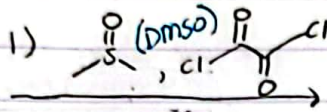
Orgo Exam #1 Notesheet

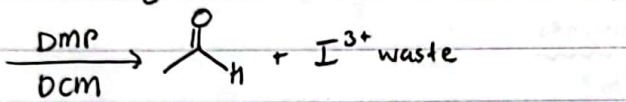
Oxidizing Alcohols

*no water ≠ carboxylic acid

PCC =  + CH_2Cl_2

Greener Alternatives

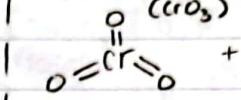
1) 
2) NEt_3



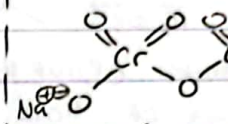
DMP / DCM

+ I^{3+} waste

Aqueous Chromium Reagents



(CrO_3) + H_2SO_4, H_2O

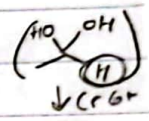


+ H_2SO_4, $-H_2O$

($Na_2Cr_2O_7$)

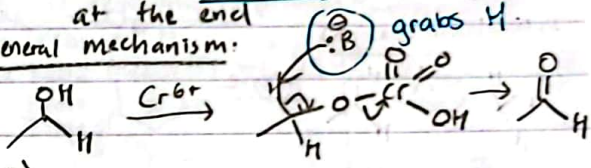
*mechanism uses H_2O alot!

*involves an elimination at the end



↓ Cr^{6+}

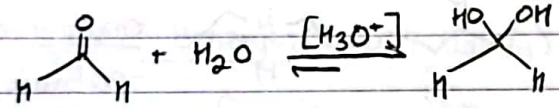
General mechanism:

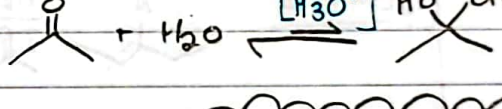


grabs H

- aldehydes = more reactive than ketones (think electronics & sterics)

- **Oxygen Nu's: Formation of Hydrates (gem-diols)**
  - uses H_2O + $[H_3O^+]$



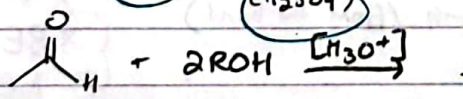


*mechanism uses H_2O ALOT!

*remember charges in mechanisms!

*think about what you're making!

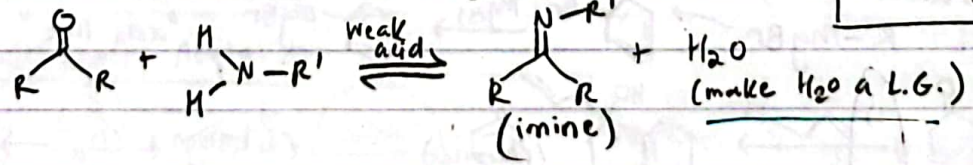
- **Oxygen Nu's: Formation of Acetals**
  - uses ROH + $[H_3O^+]$ + formation of H_2O



(H_2SO_4) (make H_2O a L.G.)

R'	functional group named
alkyl	imine
-OH	oxime
$-NR_2$	hydrazone

- **Nitrogen Nu's: 1° Amines**
  - weak acid + formation of H_2O

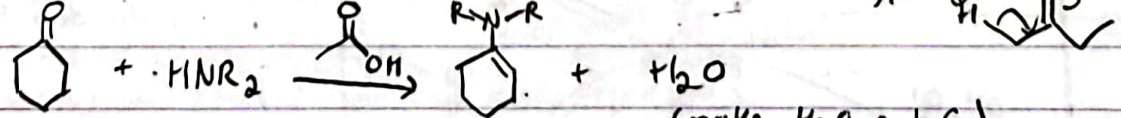


(imine) (make H_2O a L.G.)

- **Nitrogen Nu's: 2° Amines** (features an elimination rxn)

*manipulate ROH & H_2O!

  - weak acid + formation of H_2O



(enamine) (make H_2O a L.G.)

flip!

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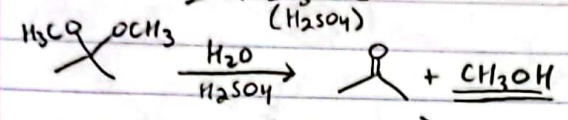
PHOR H_2O
BOH PH_2O
$P{=}H_2O$

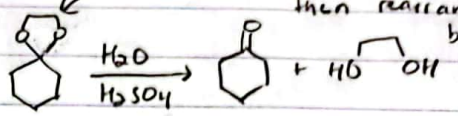
Orgo Exam #1 Notesheet

• Hydrolysis of Acetals

Hydrolysis = forming ketone again!

◦ uses H_2O & $[H_3O^+]$ (H_2SO_4)





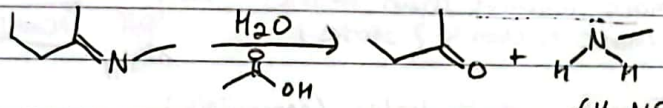
◦ mechanism (PHOR H_2O)
- protonate OR, HOR leaves, H_2O attacks

* HOR leaves (2nd time) too!

• Hydrolysis of Imines / Enamines

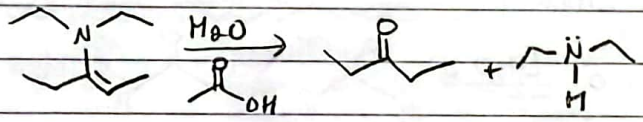
◦ uses H_2O + 

imine:

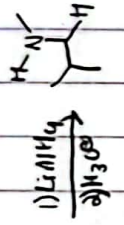


imine mechanism (PH$_2$O)
- protonate N, attack w/ H_2O
*will need to reprotonate N!

enamine:

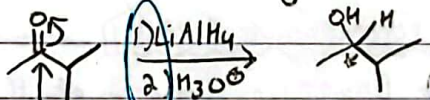


enamine mechanism (P=H_2O)
- protonate double bond, not N, N (resonance)
- moves a lone pair



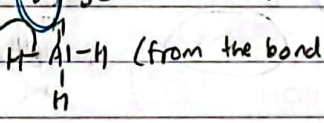
Hydrogen Nu's (can reduce ketones, aldehydes, imines)

$Li^{\oplus}\ AlH_4^{\ominus}$ $Na^{\oplus}\ BH_4^{\ominus}$



racemic - not stereospecific reaction

must be 1) then 2), otherwise $H_3O^{\oplus}$ will react w/ $H:^{\ominus}$ to give H_2 (g)

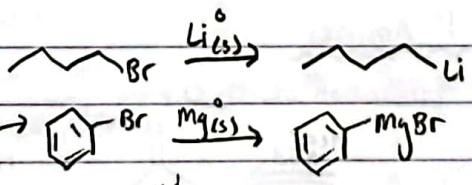


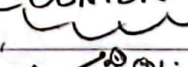
(from the bond)

*BE WARY OF NEW CHIRAL CENTERS!

Carbon Nu's

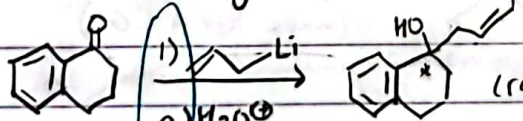
R-Li R-MgBr



"acts like" 

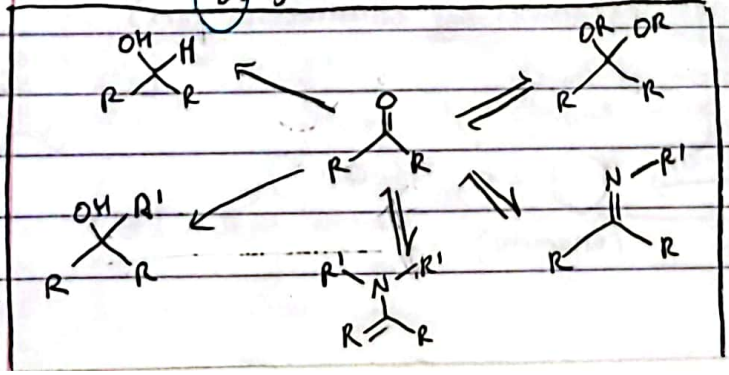
"acts like" 

Making Alcohols



Carbanion + CO_2 → carboxylic acid

RLi & RMgBr are NOT compatible w/ acidic functional groups (will deprotonate first)



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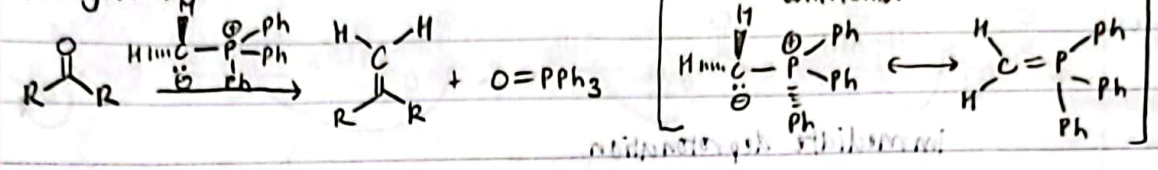
*count your carbons & mark all new chiral centers!

*label α & β positions / identify your product!

Orgo Exam #2 Notesheet

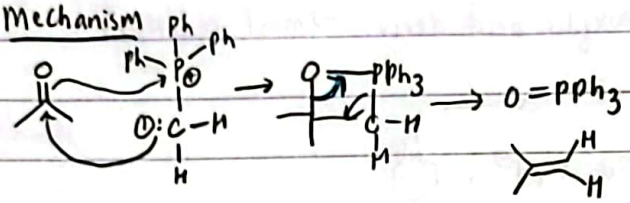
Wittig Rxn

*lock & key!

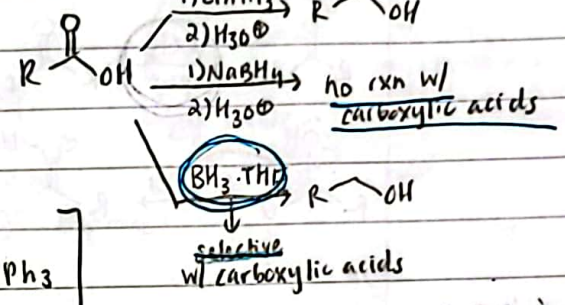


Mechanism

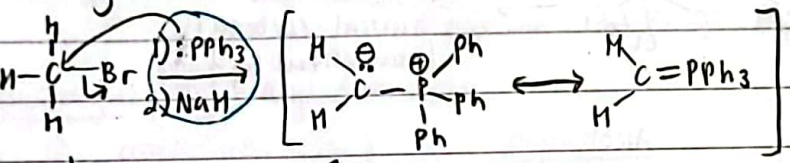
*mechanism only w/o stereochem!



Reduction of Carboxylic Acids



Making the Ylide (1° alkyl halide)



*make sure molecule is actually E or Z!

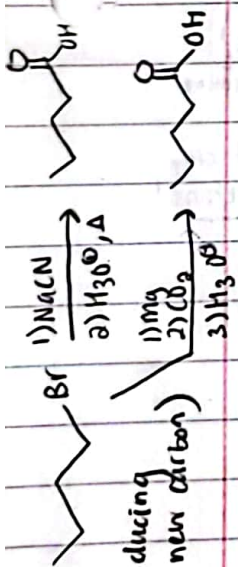
*Ylides w/ EWG → stabilized (reacts slow) → E isomer (entgegen)

↓ drawn w/ largest resonance contributor, see if you can do resonance

simple ylide → Z isomer (unstabilized)

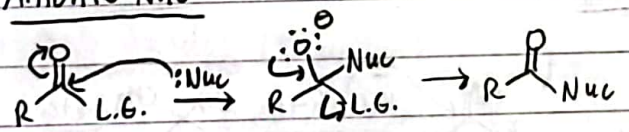
Stability ⊕, (zusammen) reactivity ⊖

(introducing a new carbon)

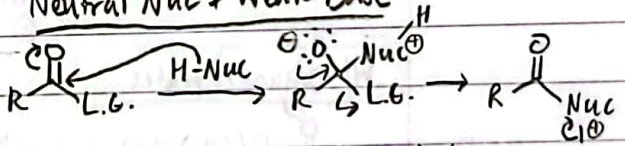


Acyl Transfer Mechanisms

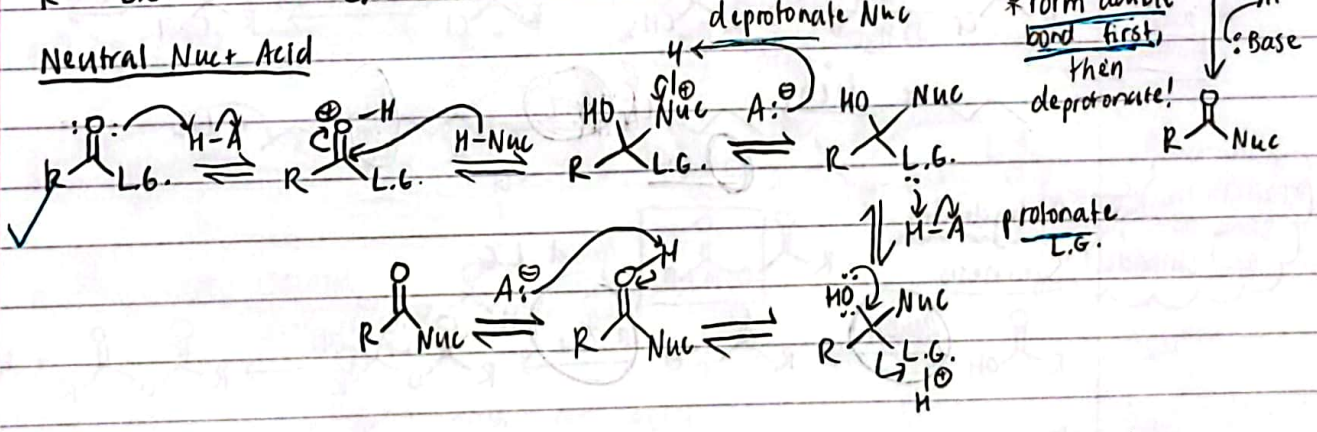
Anionic Nuc



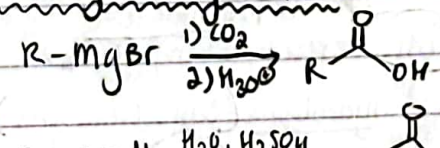
Neutral Nuc + Weak Base



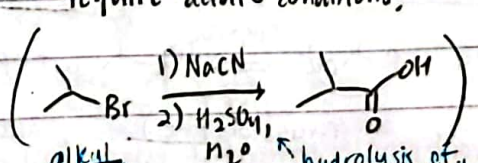
Neutral Nuc + Acid



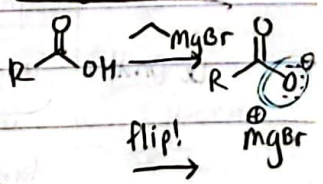
Making Carboxylic Acids



*acyl transfer rxns w/ carboxylic acid typically require acidic conditions!



Deprotonating carboxylic acids



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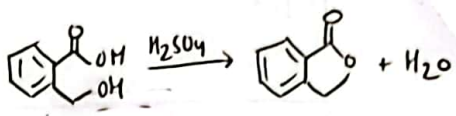
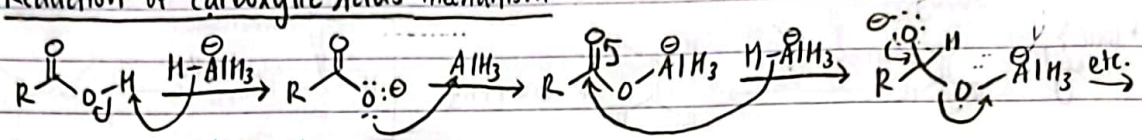
Intramolecular Ester Rxn: 

Orgo Exam #2 Notesheet

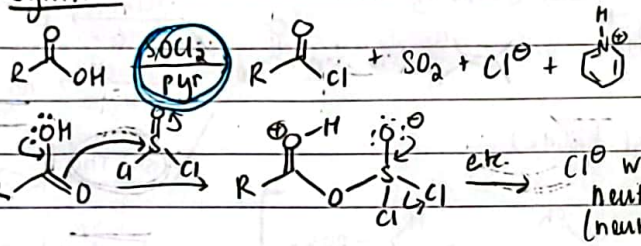
Reduction of Carboxylic Acids Mechanism



immediate deprotonation

Acid Chlorides (most E⊕ carboxylic acid deriv. → most reactive)

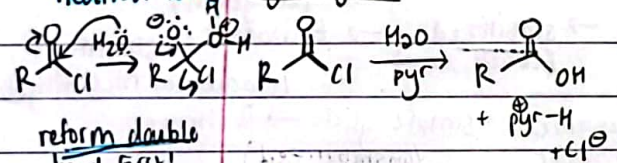
Synthesis



Cl⊖ will attack neutral carbonyl (neutralized by pyr)

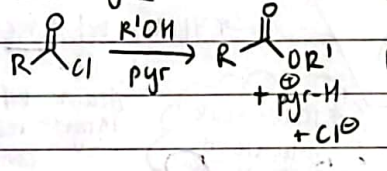
Weak base + neutral Nuc

Hydrolysis

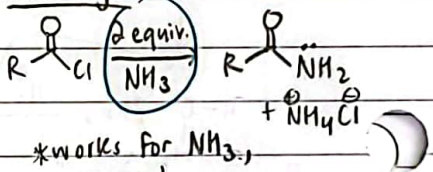


reform double bond first! then deprotonate

Alcoholysis

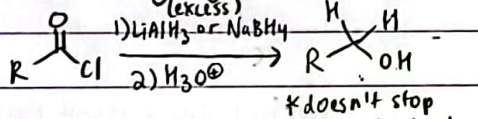


Aminolysis



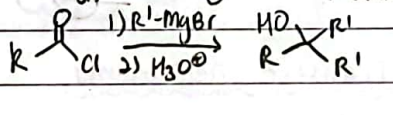
*works for NH_3, H_2NR' (1° amine), HNR'_2 (2° amine)

W/ Reducing Agents



*doesn't stop @ aldehyde

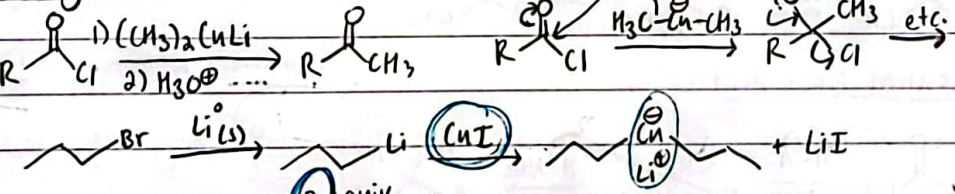
W/ Grignard Reagents



doesn't stop @ ketone!

W/ Organocuprates

*start w/ acid chloride!

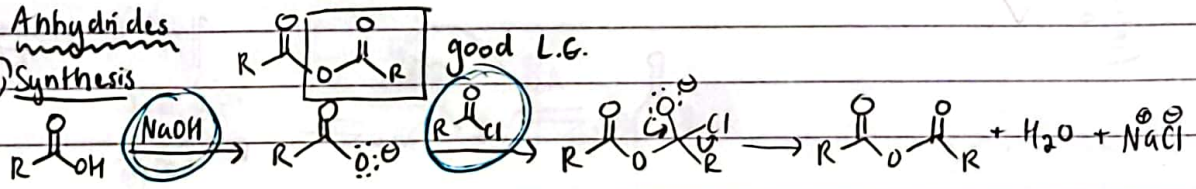


2 equiv

Anhydrides

*reacts the same as acid chlorides!

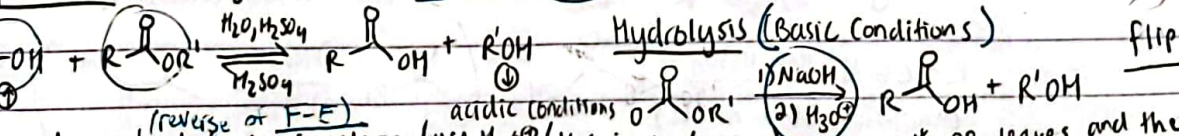
Synthesis



Esters

Synthesis: alcoholysis of acid chlorides, fisher esterification, or S_N2 (use a protonated alc. to protonate C=O)

Le Chat:



forward rxn: hydrolysis of esters (reverse of F-E) (use $H_3O^⊕$/H_2O in mechanism)

Hydrolysis (Basic Conditions)

acidic conditions

*-OR leaves and then deprotonate -OH group

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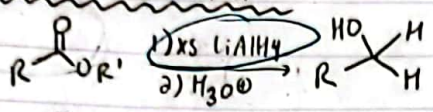
Orgo Exam #a Notesheet

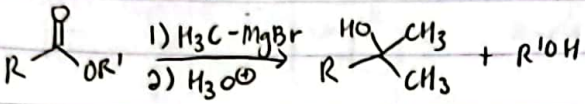
Esters Continued...

W/ Reducing Agents



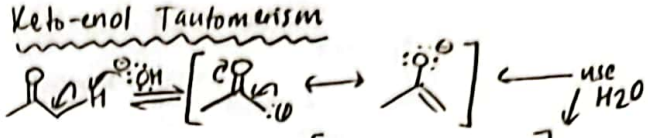
* -OR leaves!
↳ grabs H from $H_3O^{\oplus}$

W/ Grignard Reagents

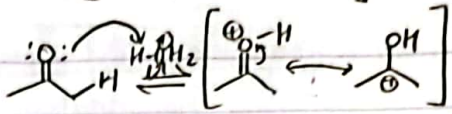


Keto-enol Tautomerism

Basic Conditions:



Acidic Conditions.



Charge: + > neutral > − (more acidic)

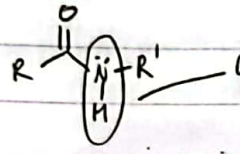
Atom: eN or size

Resonance

Induction: e⁻ donating/withdrawing effects of alkaky groups

more stable conj. base = stronger acid

Amides

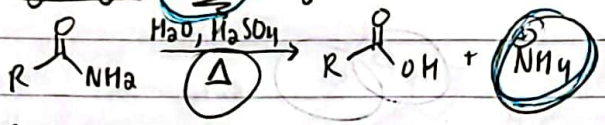


amide
N = acidic, grignard reagents will deprotonate

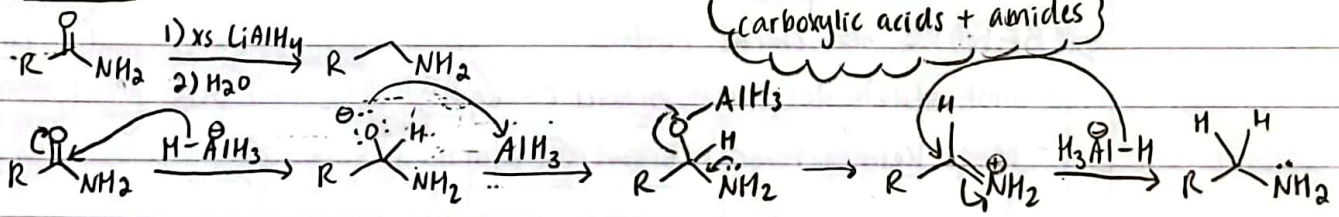
Synthesis
Aminolysis w/ 2 equiv. HNR'_2 (2° amine)

Hydrolysis (acidic acyl transfer)

hydrolysis of amides (acidic) + heat

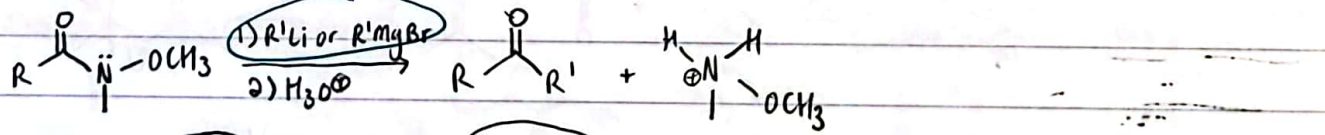


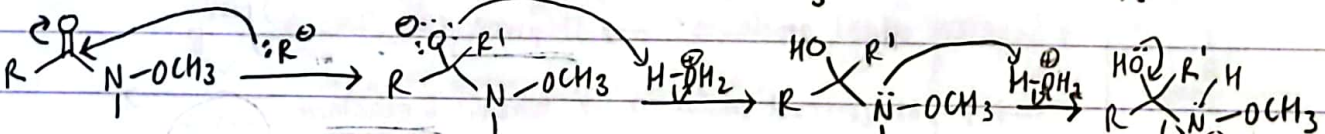
Reduction

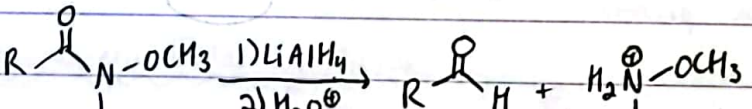


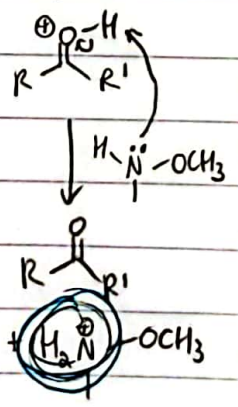
* formed a complex for reduction of carboxylic acids + amides

Weinreb Amides (Reduction)









- Using pKas? → compare acid + conj. acid

$K_a = \frac{[A^-][H^+]}{[HA]}$

$pK_a = -\log K_a$

$K_a = 10^{-pK_a}$

large K_a = lots of H^+ (strong acid)

small K_a = lots of HA (weak acid)

small pK_a = large K_a = strong acid

high pK_a = weak acid

$K_{eq} = 10^{\Delta pK_a}$ (+) → products favored or (−) → reactants favored

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3/30/23

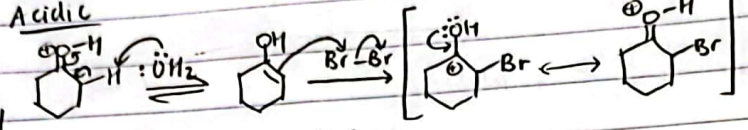
Orgo Exam #2 Notesheet

Forming enolates (irreversibly): NaH, LDA, $LiN(iPr)_2$, DEE

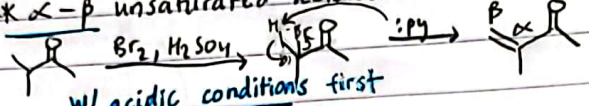
"double-α proton"

Alpha-Halogenation

Acidic



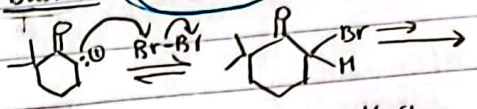
Br goes to more substituted α pos!



* α-β unsaturated ketone

w/ acidic conditions first then py!

Basic (Br_2, NaOH)

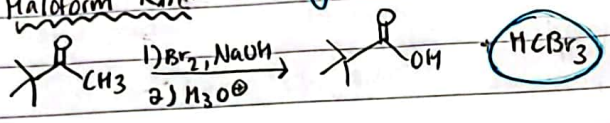


resonance

*can't stop @ 1 Br

*1 α-carbon has no H's!

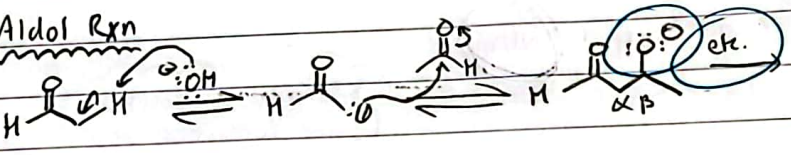
Haloform Rxn:



* after $-CBr_3$ is ejected, it deprotonates -OH group

(like hydrolysis of esters (basic))

Aldol Rxn



β-hydroxy aldehyde

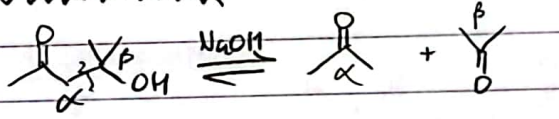
*draw a line from lone to $E^{\oplus}$, then add OH group; manipulate enolate when drawing!

★BEWARE new chiral centers

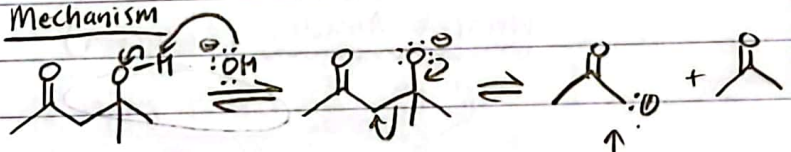
- most aldehydes favor product @ eqm
- most ketones favor reactant @ eqm

Retro-Aldol Rxn

*think about what your enolate & $E^{\oplus}$ is!



Mechanism

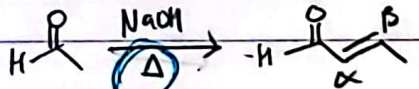


protonate w/ H_2O

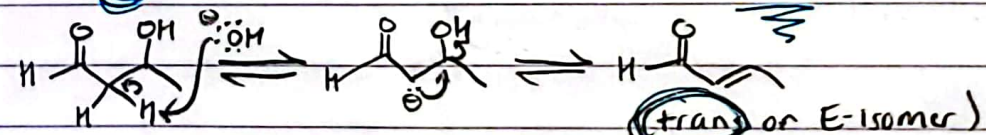
* Crossed aldol products? → stepwise rxn i.e. 1) LDA 2)  3) H_2O

↳ 1-pot crossed aldol is ok when 1 reactant has no α-protons

Aldol Condensation (forms H_2O)



trans!



(trans or E-isomer)

"$E1_{cB}$"

* Intramolecular?

↳ count C's from enolate to $E^{\oplus}$, draw shape first + attach groups!

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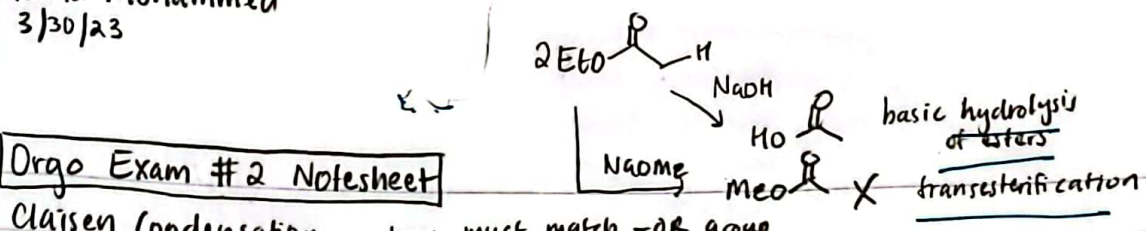
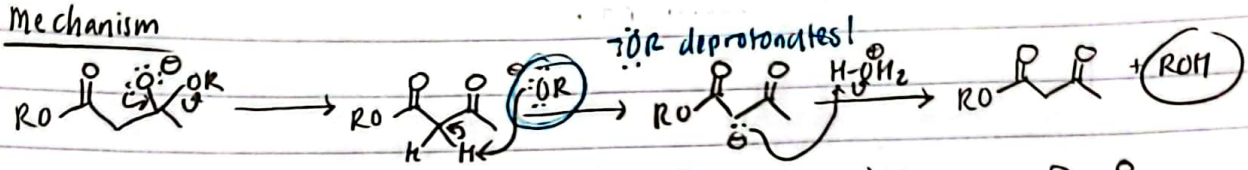
Orgo Exam #2 Notesheet

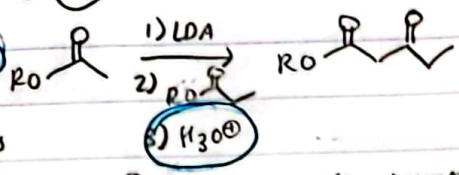


Claisen Condensation

Mechanism

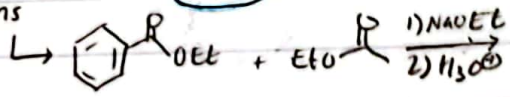


* Crossed Claisen products → stepwise rxn (ie)

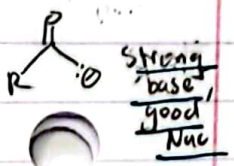


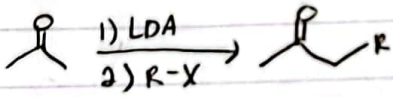
* Intramolecular?
  ↳ Make sure to deprotonate α-position again!

OR → one reactant has no α-protons



α-Alkylation w/ Enolates

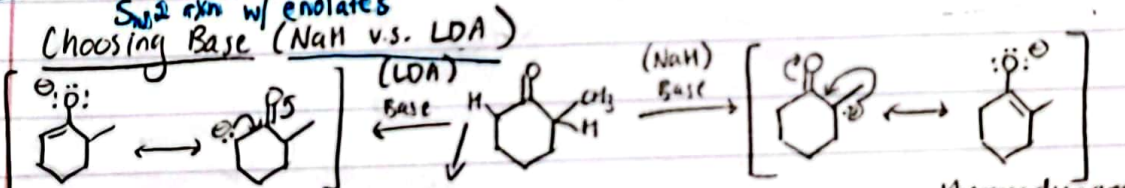




* S_N2 w/ enolate → 2° or 3° → E2 rxn
  normal restrictions apply!

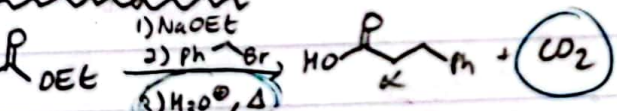
S_N2 rxn w/ enolates

Choosing Base (NaH v.s. LDA)



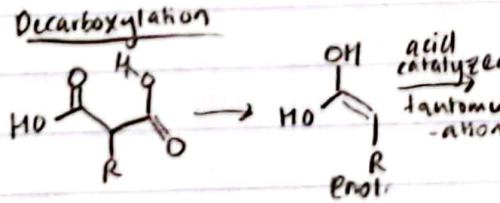
more substituted alkene = more stable enolate

Malonic Ester Synthesis

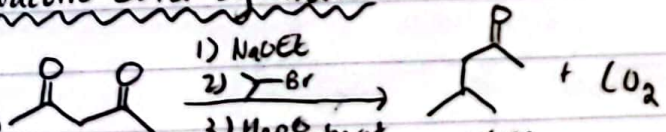


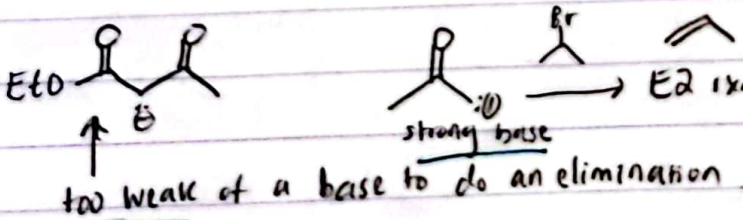
Forms -OH groups (reverse of F-E)

Decarboxylation



Acetoacetic Ester Synthesis





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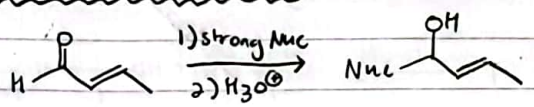
4/27/23

Orgo Exam #3 Notesheet

*count your carbons, look for new chiral centers, remember + En/double bond on diene!

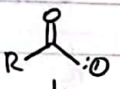
1,2- v.s. 1,4-addition



$LiAlH_4$, $RMgBr$

$^\ominus{:}\ddot{O}R$, HNR_2, R_2CuLi, (amine)

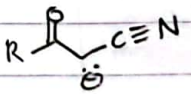
(enolate)



mix of products

(doubly stabilized enolate)

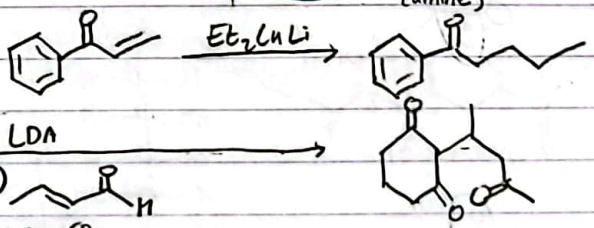
Michael donors



aldol condensation

$NaOH, \Delta$

Michael addition



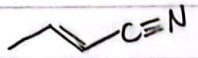
Claisen condensation

1) NaOR
2) $H_3O^\oplus$

-OR leaves & deprotonates

Michael acceptors

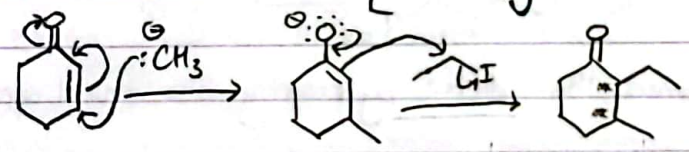
(α-β unsaturated C=O)



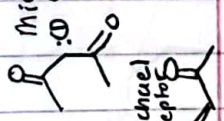
can't be a carboxylic acid (will be deprotonated)

*make sure it's 1 equiv. of $H_3O^\oplus$

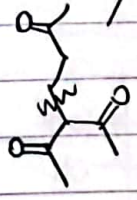
Will hydrolyze!



Michael donor



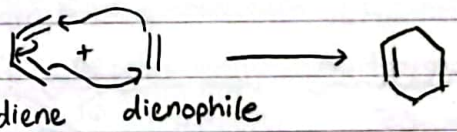
Michael acceptor



*less eN → better EDG!

Diels-Alder Rxn

*look for meso compounds!



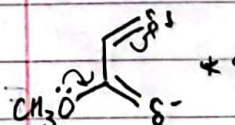
diene dienophile

diene must be..
- conjugated
- s-cis conformation

*think of steric hinderance of s-cis conformation of diene! (for rxn rate)

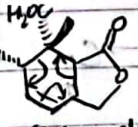
- more e^- rich diene and/or e^- poor dienophile → faster rxn
- EDG near δ^+, EWG near δ^-

↓ exception:



* δ^+ away from EDG

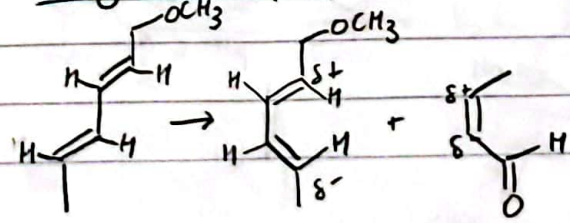
Strategy:
1) Rotate diene to s-cis conformation
2) Label partial charges + line up regiochem
3) Use "in/out" rule to determine stereochem.
* EWG = "out" on dienophile

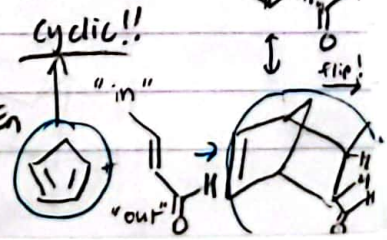


(intramolecular)

out = ||||
in = —

- Resonance > induction for electronic stability
- Strongest EDG/EWG takes priority when assigning partial charges





SAME

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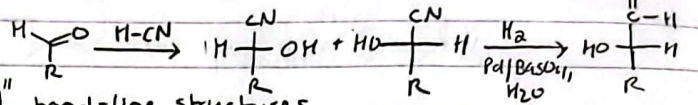
4/27/23

*check every chiral center before describing relationship!

Orgo Exam #3 Notesheet

Historical formula: $C_n(H_2O)_n$

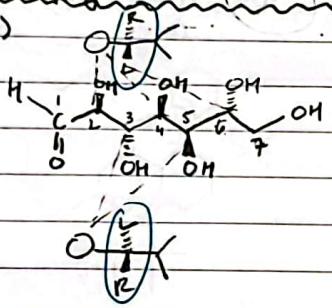
Chain Lengthening



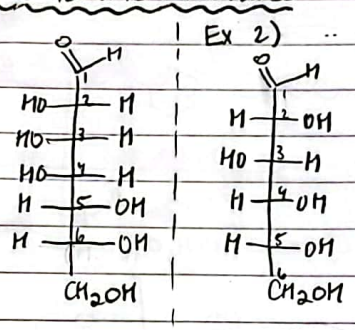
Fischer projections ⇌ "Normal" bond-line structures

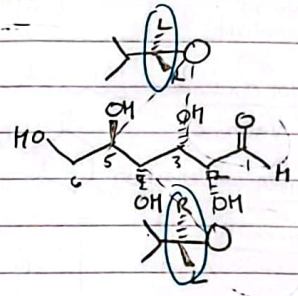
-align head w/ carbonyl
-start w/ top then bottom

Ex 1)

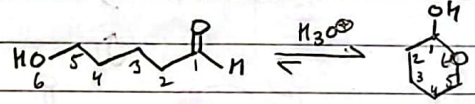


Ex 2)





- D & L sugars w/ same name ⟶ enantiomers
  - -OH on right
  - -OH on left

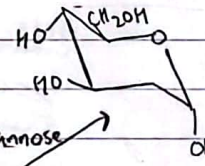


*R Config. when -OH = right

- Epimers – diastereomers that differ by exactly one chiral center (specify location) *even normal chains

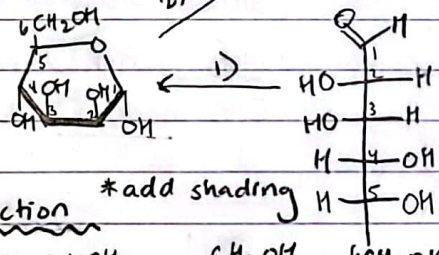
type of diastereomer (ring only)

- Anomers – differ in configuration of anomeric carbon only
  - α (trans), β (cis)



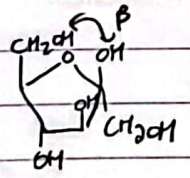
- Fischer projection ⟶ Haworth projection
  - If D-sugar, put $-CH_2OH$ up on C5 (down if L-sugar)
  - place -OH on anomeric carbon (C1)
    - ↳ based on α & β assignments

Draw α-D-Mannose

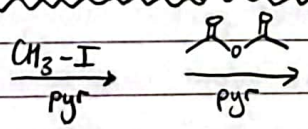


for -OH groups:
right = down
left = up

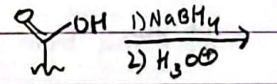
D- to L-sugar? chair flip!



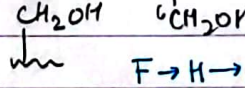
- Reactions of Carbohydrates



- Reduction

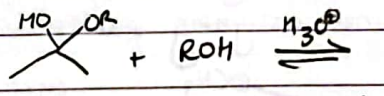


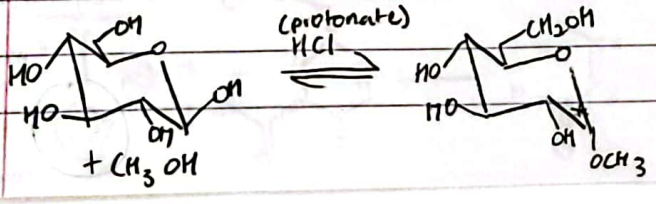
*add shading



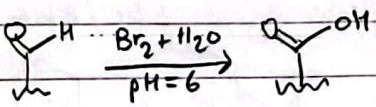
F → H → C

- Glycoside formation





- Oxidation



flip!

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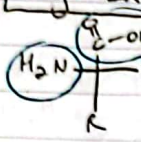
4/27/23

pH < pKa protonate [HA]
pH > pKa deprotonate [A⁻]

Orgo Exam #3 Notesheet


amino acid as Fischer projection

*20 diff side chains commonly found in organisms!
L-amino acids!

*Start fully protonated!
↳ start w/ right side when doing ZI of peptide

R group: nonpolar / polar (can H-bond) / acidic / basic (or neither)

acidic side chains – carboxylic acids

basic side chains – amine/imine

$HA \rightleftharpoons H^+ + A^-$

$K_a = \frac{[H^+][A^-]}{[HA]}$

• $pH = -\log[H^+]$ describes H^+ content in sol.

v.s.

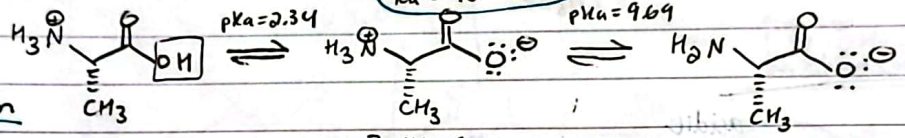
$pK_a = -\log(K_a)$ describes acidity of a molecule or part of a molecule

$pH = pK_a + \log\frac{[A^-]}{[HA]}$

if $[A^-] = [HA]$, $pH = pK_a$

• Isoelectric point – pH where Zwitterion is most prevalent (neutral form)

Ex 1)



pH < 2.34 | Zwitterion | pH > 9.69

When calculating pI: pKa's need to be on either side of Zwitterion

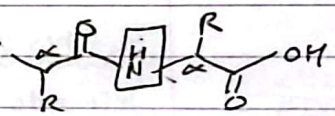
$pI = \frac{2.34 + 9.69}{2}$

pI = 6.02 max conc. of Zwitterion when pH = 6.02

∘ Shortcut: when 3 pKa's involved → pI = avg. of 2 most similar pKa's

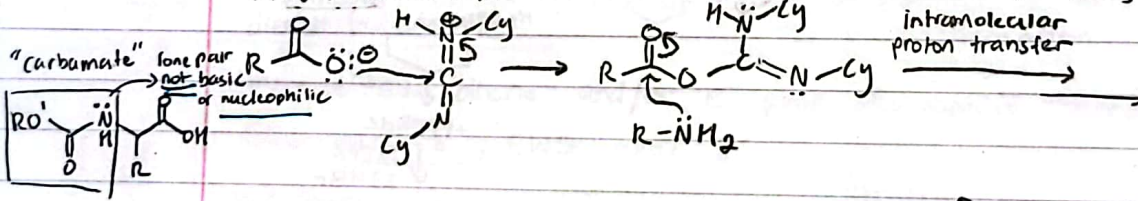
• Drawing Peptide Chains

1) Draw N-terminus on left side (N, α, C)
2) Add R groups to α carbons (use chart → check C's)
3) Add stereochem (L-amino acids only)



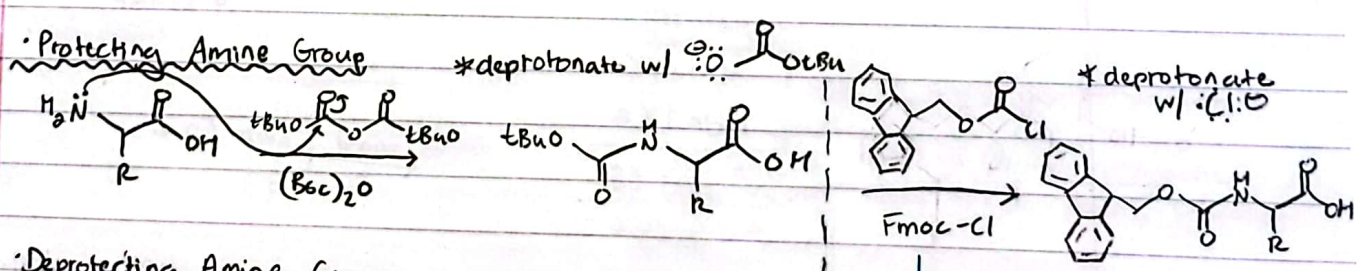
R group "up" – wedge
R group "down" – dash

• DCC Mechanism

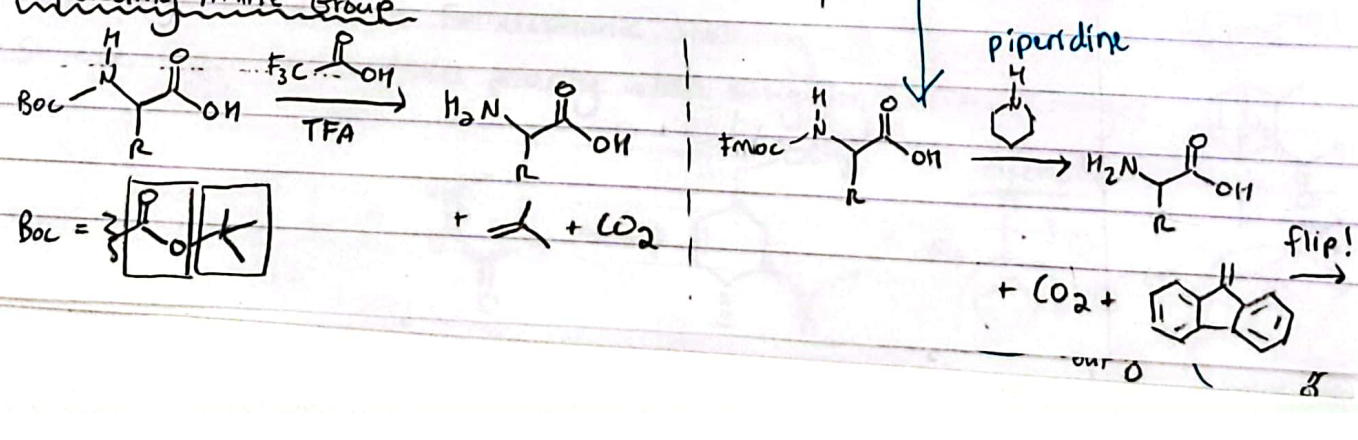


then 3 arrows!
DCC ≠ catalyst

• Protecting Amine Group



• Deprotecting Amine Group



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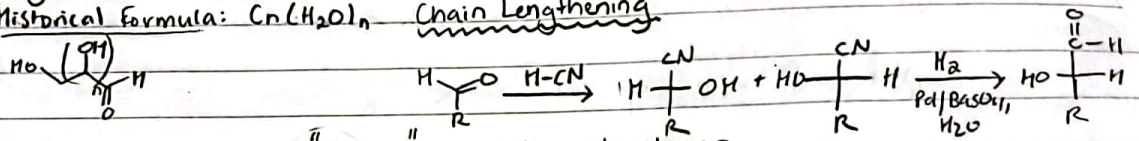
*check every chiral center before describing relationship!

Orgo Exam #3 Notesheet

Historical Formula: $C_n(H_2O)_n$

Chain Lengthening



Fischer projections ⇌ "Normal" bond-line structures

-align head w/ carbonyl
-start w/ top then bottom

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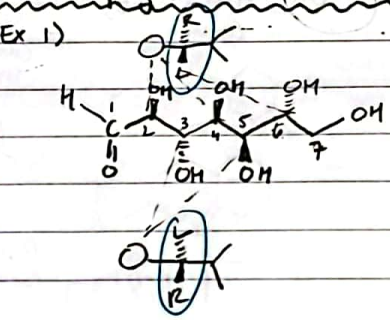
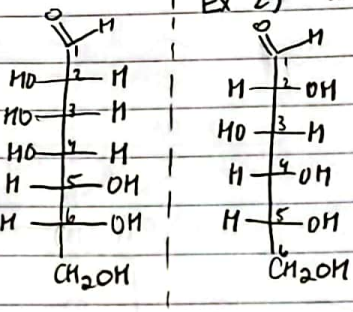
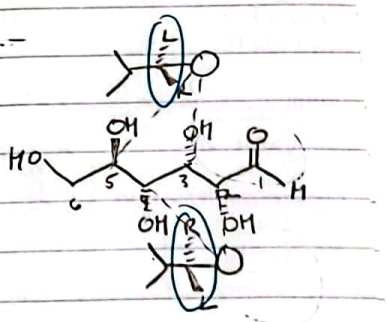
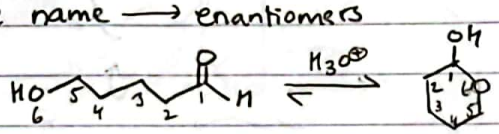


Ex 2)





- D & L sugars w/ same name ⟶ enantiomers
  - -OH on right
  - -OH on left



*R config. when -OH = right

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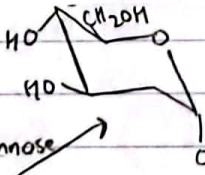
- Anomers – differ in configuration of anomeric carbon only (type of diastereomer ring only)
  - α (trans), β (cis)



- Fischer projection ⟶ Haworth projection

for -OH groups:
right = down
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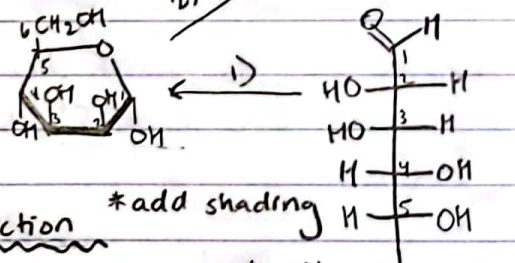
  - ↳ based on α & β assignments

Draw α-D-Mannose



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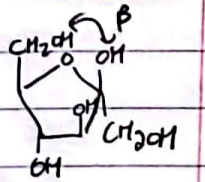
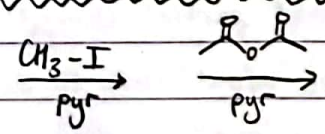
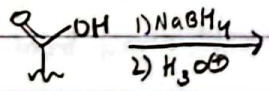
D- to L-sugar? chair flip!



- Reactions of Carbohydrates

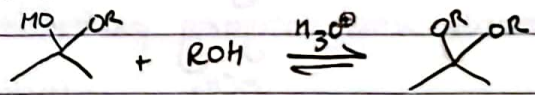


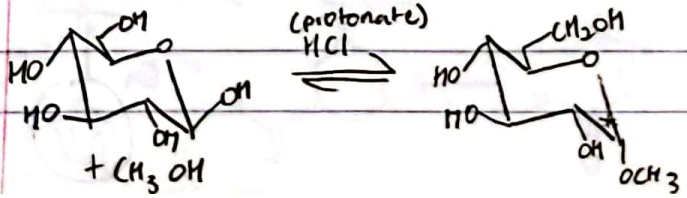
- Reduction



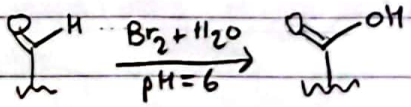
F → H → C

- Glycoside formation





- Oxidation



flip!

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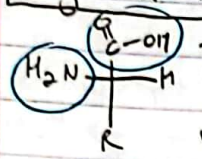
4/27/23

pH < pKa protonate [HA]
pH > pKa deprotonate [A⁻]

Orgo Exam #3 Notesheet



*Start fully protonated!
↳ Start w/ right side when doing ZI of peptide

*20 diff side chains commonly found in organisms!
L-amino acids!

R group: nonpolar / polar (can H-bond) / acidic / basic (or neither)

$HA \rightleftharpoons H^+ + A^-$

- $pH = -\log[H^+]$ v.s. $pK_a = -\log(K_a)$ $K_a = \frac{[H^+][A^-]}{[HA]}$

$pH = pK_a + \log\frac{[A^-]}{[HA]}$

pH: describes H^+ content in sol.

pKa: describes acidity of a molecule or part of a molecule

acidic side chains - carboxylic acids

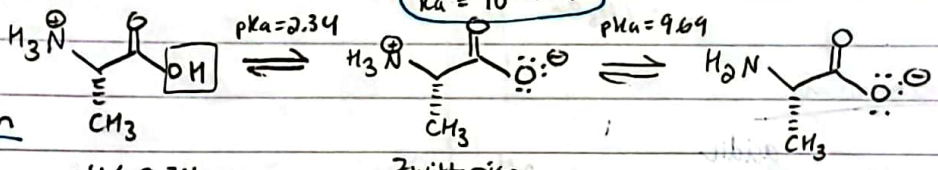
basic side chains - amine/imine

if $[A^-] = [HA]$, $pH = pK_a$

- Isoelectric point - pH where Zwitterion is most prevalent (neutral form)

When calculating pI: pKa's need to be on either side of Zwitterion

Ex 1)



pH < 2.34 | Zwitterion | pH > 9.69

$pI = \frac{2.34 + 9.69}{2}$

pI = 6.02 max conc. of zwitterion when pH = 6.02

- Shortcut: when 3 pKa's involved → pI = avg. of 2 most similar pKa's

- Drawing Peptide Chains

1) Draw N-terminus on left side (N, α, C)
2) Add R groups to α carbons (use chart → check C's)
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R group "up" - wedge
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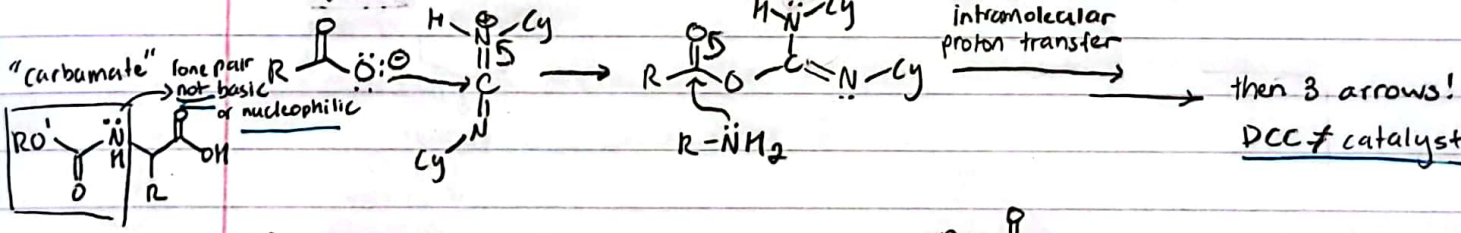
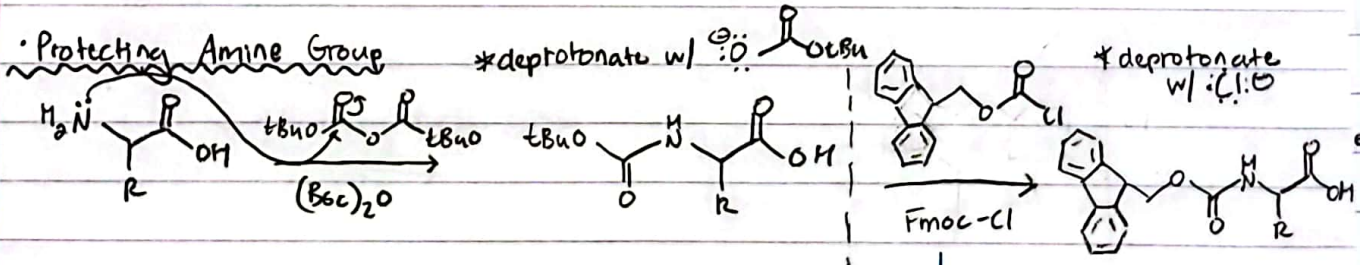
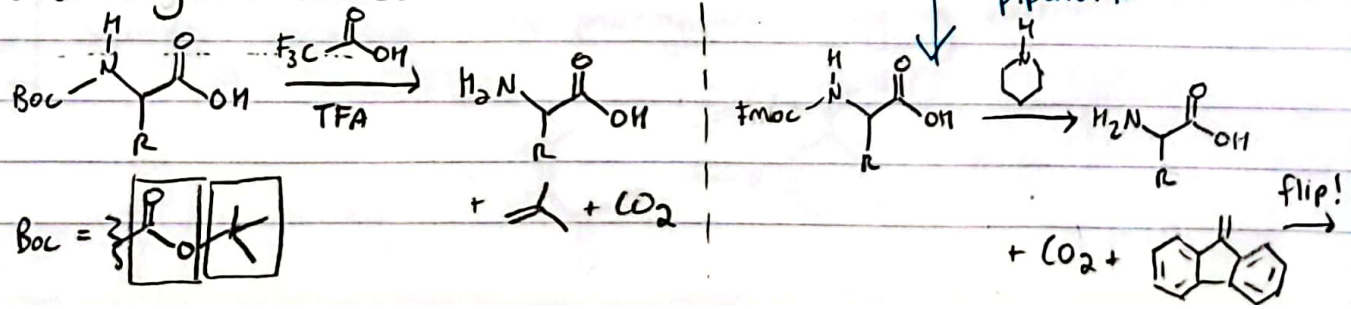
- DCC Mechanism



- Protecting Amine Group



- Deprotecting Amine Group

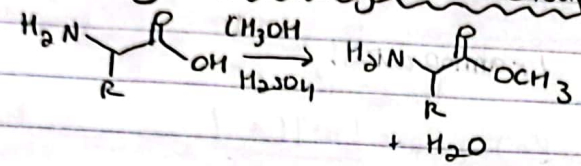


Nuha Mohammed
4/27/23

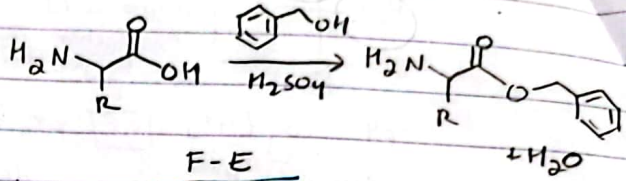
Orgo Exam #3 Notesheet

*look at back at your steps for peptide synthesis, make sure it makes sense!

Protecting the Carboxylic Acid Group



F-E

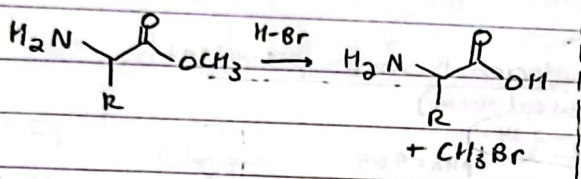


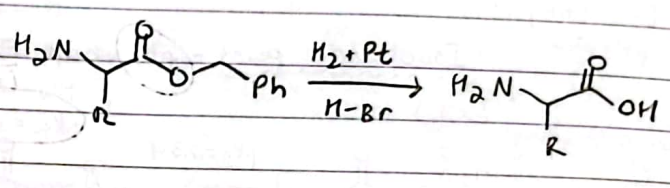
F-E

- not acidic
- weak E⊕, won't be attacked by N
- won't attack DCC (no $\ddot{O}^{\ominus}$)

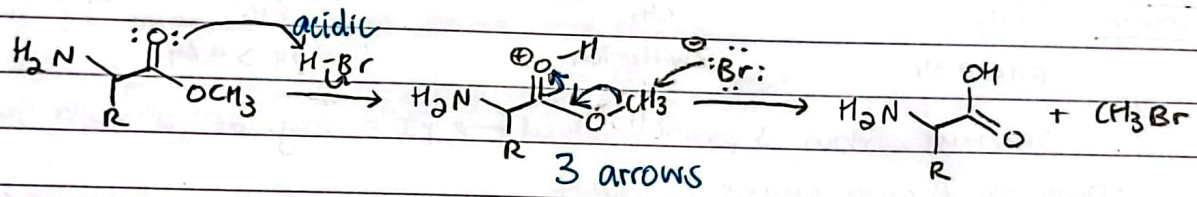
Deprotecting the Carboxylic Acid Group

for F-E
- deprotonate
- protonate -OH group





HBr Mechanism



3 arrows

Synthesizing Peptides

left side amino acid → protect w/ $(Boc)_2O$

right side of amino acid → protect w/ CH_3OH, H_2SO_4

→ DCC → peptide → deprotect 1) TFA 2) HBr

If there's a 3rd amino acid → protect w/ CH_3OH, H_2SO_4, deprotect dipeptide w/ HBr

→ DCC → peptide → 1) TFA 2) HBr